September 28,1999

MEMORANDUM

SUBJECT: RESPONSE TO COMMENTS: HED Response to Comments Concerning the EPA Preliminary Human Health Risk Assessment for Ethyl Parathion. Bar Code: D260106

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This memorandum has been prepared as a response to comments received by the Agency concerning the parathion preliminary human health risk assessment and supporting science documents. This response addresses parathion-specific comments and will not address comments received by the Agency that are considered generic to the organophosphate pesticides.

The preliminary risk assessment for parathion was first released to the registrant (Cheminova) on November 4, 1998, and to the public docket on January 15, 1999. On December 4, 1998 the Agency received comments from Cheminova in response to the draft parathion human health risk assessment (dated 10/28/98) and other docketed material including the HIARC report, the residue chemistry chapter, and the occupational risk assessment. The intent of the first phase was to allow Cheminova to correct "mathematical, computational, typographic, or other similar errors". HED acknowleged receipt of comments and its intent to correct (agreed upon) errors for the revised (phase 4) risk assessment (N. Paquette memo, January 12, 1999). In addition to comments addressing errors, the Cheminova submission of 12/4/98 also contained substantial comments addressing "errors in applicability of data and flaws in data

analysis". Subsequent to the 12/4/98 submission, the Agency received on March 16, 1999 additional comments from Cheminova concerning the preliminary parathion human health risk assessment.

As stated above, errors identified in the preliminary risk assessment and supporting discipline chapters have been addressed in the revised risk assessment for phase 4. This response will address comments, other than error corrections, received in the two submissions listed above and will be limited to comments that could directly affect the parathion risk assessment through changes in endpoint selection, dose selection, exposure estimates, etc. Agency decisions or policies concerning the regulation of cholinesterase inhibiting chemicals, or other related issues concerning risk assessment, are not discussed in this response.

In general, Cheminova has commented to all aspects of the human health risk assessment, which is comprised of hazard identification (toxicology) , dose response and endpoints for risk assessment, residue chemistry, dietary exposure, occupational exposure, dietary and occupational risk estimates, and risk characterization. Cheminova comments are organized in this fashion and this HED response will address the same general areas without necessarily listing or addressing each specific comment.

Cheminova's comments are preceded by a discussion of the use of Confidential Business Information (CBI) in the draft RED chapters and a request for the removal of any references to unregistered formulation(s) in the revised risk assessment. The Cheminova submission also contains a clarification of the ethyl parathion food/feed use sites, use patterns, and label restrictions which Cheminova intends to support for reregistration. Specifically, Cheminova summarizes the 1991 Agreement with EPA (to address worker exposure), current Cheminova registrations for technical parathion and end-use products, the amount used per crop, and directions for use. This information has been carefully considered by the Agency since certain information is an integral part of the risk assessment.

TOXICOLOGY AND ENDPOINTS FOR RISK ASSESSMENT

Cheminova submitted two documents on the preliminary risk assessments for parathion (December 4, 1998 and March 26, 1999). For the purposes of a consolidated response, the toxicology related comments have been combined and will be addressed according to the issues raised.

A. Data Submissions and Data Evaluations

Cheminova submitted an acute dietary neurotoxicity study in rats (*D257406)* using a new (non-guideline) protocol in which the potential for acute neurtotoxicity was

evaluated following a one-time dietary administration over a one hour period. The new feeding protocol has also been submitted for two other chemicals, and together the studies underwent peer review (Science Advisory Panel, July 21, 1999). The results of the Panels recommendations have not been received by the Agency. The study is still in review and will not be evaluated in the context of the current risk assessment.

Cheminova disagrees with HED's interpretation of many of the guideline studies described in the Hazard Identification Assessment Review Commitee's (HIARC) April 27, 1999 memo. Cheminova provides alternative interpretations of the data, including arguments concerning the relevance of cholinesterase inhibition in endpoint selection. HED noted Cheminova's interpretation of the study summaries. The studies and the relevance of cholinesterase inhibition were reviewed in accordance with HED policy and have completed internal review. In cases where HED agreed that study conclusions were misrepresented in the HIARC memo or that statements could be misinterpreted, HED corrected or clarified the statements. The issues raised by Cheminova did not affect the endpoints used for the ethyl parathion risk assessment.

Cheminova objected to many of the endpoints selected for the risk assessment. Cheminova believed that the endpoints chosen overestimate risk and suggested alternative studies or endpoints for use in particular risk scenarios. HED evaluated Cheminova's proposal and several issues raised by Cheminova. The results are discussed individually in this document and in the revised risk assessment.

Cheminova believed that the dermal absorption factor of 100% estimated by HED for dermal risk assessments is too high. HED's estimation of 100% is based on 1) parathion is highly acutely toxic with similar LD_{50} across several species regardless of route of administration; 2) comparing the LOAELs established in the acute oral and dermal toxicity studies based on the same toxicological endpoint in the rat; 3) evaluating the physical or chemical properties of the pesticide (i.e., granular, emulsified concentrate, water solubility, etc.); 4) the use of structure activity relationship (i.e., examining the similarity of parathion to its homolog, methyl parathion); and 5) a 21-day dermal toxicity study in rats was not available. This decision was reaffirmed in the HIARC meeting of 2/24/99 (see attached memo; HED Doc # 013270).

Acute Population Adjusted Dose

Previously, the HIARC had selected the acute oral neurotoxicity study for use in acute dietary risk assessment (HIARC Report, 4/27/98). Effects seen at 2.5 mg/kg in male and female rats in this study included plasma, red blood cell (RBC) and brain cholinesterase inhibition and changes in functional observation battery and motor activity in females. The NOAEL from this study was set at 0.025 mg/kg in male rats and 0.5 mg/kg for female rats. The male rat NOAEL of 0.025 mg/kg was selected instead of the female rat NOAEL of 0.5 mg/kg for the acute dietary risk assessment based on the

effects seen at the next highest dose in male rats (LOAEL = 2.5 mg/kg). Because the mid and low doses used in this study in male rats differed by a factor of 100, the registrant requested reconsideration that the NOAEL from the female rats (0.5 mg/kg) be used for the acute dietary risk assessment.

On August 12, 1999, the Hazard Identification Assessment Committee (HIARC) evaluated available data for parathion, and agreed with the registrant that the NOAEL for female rats (the most sensitive sex) was 0.5 mg/kg. However, there was an 8% decrease in red blood cell cholinesterase activity in this group compared to control which could not be dismissed. While this inhibition was slight and not statistically significant there was support of a similar effect in a 1991 pilot study (MRID 41834501), in which female rats (2 rats/dose) given 0.25 mg/kg and 0.5 mg/kg had approximately 30% and 40% decreases in plasma cholinesterase, respectively, and approximately 6% and 8% decreases in red blood cell cholinesterase, respectively, after 1 day of treatment. The Committee had less confidence in the NOAEL of 0.5 mg/kg in female rats in light of the pilot study data and the slight decrease in red blood cell cholinesterase in the selected acute neurotoxicity study. Furthermore, while the Committee acknowleges that there was no dose between 0.025 mg/kg and 2.5 mg/kg in male rats, there was still uncertainty about the effects which might occur at doses less than 2.5 mg/kg, making the dose response toxicity profile in male rats not well defined. For these reasons, the Committee had greater confidence that the NOAEL was below 0.5 mg/kg, and selected the NOAEL of 0.025 mg/kg for the acute dietary risk assessment endpoint.

Although the Committee recognized that the use of this study with a NOAEL of 0.025 mg/kg for acute dietary risk assessment was conservative, the Committee believed that the endpoint selected would not underestimate the risk for a single exposure.

Chronic Population Adjusted Dose

Cheminova concurs with the study and endpoint selected by the Agency (chronic toxicity study in dogs MRID 24664243), but disagrees that a NOAEL was not established in the study and disagrees that an additional 3-fold uncertainty factor is required. HED reiterates that there was a statistically significant decrease in RBC cholinesterase activity in male and female dogs at all dose levels including the lowest dose tested, 0.01 mg/kg bw/day. HED does not believe that cholinesterase inhibition in plasma or RBC needs to correlate to clinical signs in order to be of biological significance. HED maintains that the LOAEL in this study is 0.01 mg/kg bw/day and therefore an uncertainty factor of 3 is added for lack of a NOAEL.

Short-Term Occupational Exposure

Cheminova disagrees with the selection of the NOAEL from an acute oral neurotoxicity study in rats (MRID 43117901) as an endpoint for the short term dermal occupational exposure risk assessment. Cheminova proposes that the acute dermal toxicity study in rats (MRID 40814002) be used instead. Cheminova also disagrees with the Agency's and the study author's conclusion regarding the NOAEL for cholinesterase inhibition in this study.

The Committee also considered the registrant's proposal that the acute dermal toxicity study (MRID 40814002) should be used for the short term dermal exposure risk assessment. The current short term dermal exposure toxicity endpoint (NOAEL = 0.025 mg/kg), is based on the plasma and red blood cell cholinesterase inhibition in male rats at 2.5 mg/kg in an acute neurotoxicity study. The Committee agreed that the endpoint from the acute neurotoxicity study might not be appropriate for the short term exposure assessment. The NOAEL from the acute dermal toxicity study in rats was 0.45 mg/kg based on decreased plasma cholinesterase (10%) activity in female rats at 0.68 mg/kg (LOAEL). While this endpoint might be appropriate for a one-day dermal exposure period, the Committee believed that the use of this study would underestimate the risk for any exposure period longer than 1 day. For this reason, the Committee selected the NOAEL of 0.01 mg/kg bw/day from a six month dog toxicity study (MRID 41836601) in which plasma cholinesterase was markedly decreased in male and female dogs at the one week time period by approximately 84% and 79%, respectively, at 0.8 mg/kg bw/day (LOAEL) compared to control or pretreatment values. No other subchronic rat or dog study was available that measured cholinesterase activity at the one week time period

Intermediate-Term Occupational Exposure

Cheminova disagrees with the use of a 6-month subchronic dog study (MRID 41836601) for endpoint selection for this exposure time period and disagrees with the NOAEL of 0.0024 mg/kg bw/day. Cheminova notes that there was a 100-fold difference between the mid dose (0.01 mg/kg bw/day) and the highest dose (0.8 mg/kg bw/day) and does not believe the use of the study is appropriate. Cheminova did not provide an alternate study.

HED reaffirmed the NOAEL in the 6-month dog study to be 0.0024 mg/kg bw/day based on a reduction in plasma cholinesterase activity by Week 6 of treatment in male and female dogs given 0.01 mg/kg bw/day by 20% and 25%, respectively. Furthermore, in a shorter duration study period, a 3-month study in dogs (MRID 00071670), the LOAEL for plasma cholinesterase inhibition was 0.3 mg/kg for both male and female dogs at weeks 6 and 13 ; no NOAEL could be established. The LOAEL was 0.3 mg/kg (lowest dose tested) for RBC ChE inhibition for female dogs at

weeks 6 and 13, therefore a NOAEL could not be established. In a longer duration study, a 1 year dog study (MRID 00009386), the LOAEL was 0.01 mg/kg (lowest dose tested) based on decreased plasma and RBC cholinesterase activity in both male and female dogs at the 2 and 12 month period but not the 4 month interval. The decreases were dose related at all time points (month 2, 4, 12) but the interspecies variance was high, which may explain in part the lack of statistical significance at the 4 month period; a NOAEL was not established.

RESIDUE CHEMISTRY AND DIETARY EXPOSURE

HED has completed a revised dietary risk assessment for parathion, substantially refining dietary exposure estimates used in the previously issued preliminary dietary risk assessments for parathion. We acknowledge the registrant's many comments concerning anticipated residue estimates and will use the subject information as HED deems appropriate.

New Data

HED acknowledges receipt of the following new residue chemistry data submitted in support of the reregistration of parathion: (I) Independent Laboratory Validation (ILV) data for residues of parathion, paraoxon, and 4-acetamidoparaoxon in kidney and milk (MRID 44547401), (ii) storage stability data on field corn grain, meal, grits, flour, starch, and refined oil (MRID 44559601) and test sample storage intervals/conditions information from magnitude of the residue studies (MRID 44640501), (iii) barley grain, hay, and straw field trial data (MRID 44602201), (iv) magnitude of the residue data on aspirated grain fractions (AGF) derived from wheat grain (MRID 44590201) and sorghum grain (MRID 44591301), (v) cotton gin trash magnitude of the residue data (MRID 44594901), (vi) meat, milk poultry and egg magnitude of the residue data (MRIDs 44527301 and 44527302), and (vii) confined rotational crop data (no MRID; cover letter from Jellinek Swartz & Connolly, Inc. dated 11/12/91). These data are under review and will be used in the residue chemistry science and dietary risk assessments for parathion as the Agency deems appropriate.

Food/Feed Use Patterns

HED acknowledges receipt of clarification of the maximum food/feed use patterns and restrictions which the registrant (Cheminova) wishes to support for the reregistration of parathion on food/feed crops. This detailed use information will be carefully considered in the tolerance reassessment process and dietary risk assessment analyses for parathion.

Confidential Business Information

HED has reexamined the draft Residue Chemistry Chapter for the Parathion Reregistration Eligibility Decision (RED) (5/27/98) and expunged all possible Confidential Business Information (CBI) from future drafts of this document.

P-nitrophenol

HED reiterates that potential residues of *p*-nitrophenol resulting from the use of parathion are of concern. We would point out that none of the previously submitted parathion residue chemistry data have been rejected on the grounds that residues of *p*-nitrophenol resulting from parathion were not adequately depicted nor are future data likely to be rejected solely, or in part, on this condition.

Cumulative risk assessment for residues of p-nitrophenol

HED notes the registrant's many comments concerning the need to conduct a cumulative risk assessment for residues of *p*-nitrophenol; however, we would remind the registrant that such a decision is ultimately under the Agency's purview.

Required Data

There are no alfalfa forage and alfalfa hay magnitude of the residue data reflecting the maximum use rate of parathion on alfalfa. There are no available data deemed appropriate for translation to alfalfa. Data are required depicting parathion residues of concern in/on alfalfa forage and hay reflecting the maximum use rate of the EC formulation of parathion on alfalfa. The registrant should refer to OPPTS GLN 860.1500 for information on location and number of field trials required. Since it is unlikely that the currently established tolerances for residues of parathion in/on alfalfa forage and alfalfa hay are adequate, the required data are considered critical to tolerance reassessment. We acknowledge that the registrant (Cheminova) has committed to generate the subject data.

There are no wheat hay magnitude of the residue data reflecting the maximum use rate of parathion on wheat. There are no available data (including barley hay) deemed appropriate for translation to wheat hay. Data are required depicting parathion residues of concern in/on wheat hay reflecting the maximum use of the EC formulation of parathion on wheat. The registrant is referred to OPPTS GLN 860.1500 for information on the location and number of field trials required. Since it is unlikely that the currently established tolerance for residues of parathion in/on wheat (1 ppm) is adequate to cover residues of parathion in/on wheat hay, the required data are considered critical to tolerance reassessment. We note that the registrant (Cheminova) has <u>not</u> committed to generated these data.

Import Issues

We understand (page 86 of 127 of the registrant's 12/4/98 response) that the registrant (Cheminova) is only committed to supporting the use of parathion on alfalfa, barley, corn, canola, cotton, grain sorghum, soybean, sunflower, and wheat and the associated tolerances for these crops. They have made it clear that they will not support any other currently established tolerances for residues of parathion in/on fruits and vegetables incurred in imported commodities treated with parathion.

OCCUPATIONAL EXPOSURE

Endpoints Used To Assess Worker Exposure

Cheminova disagrees with HED's selection of an endpoint for short-term worker dermal exposure. Cheminova believes that the appropriate endpoint should be 1.35 mg/kg/day based on an acute dermal toxicity study in rats. Cheminova also disagrees with HED's selection of an endpoint for intermediate-term worker dermal exposure. Cheminova states that they will conduct a new toxicity study designed to address these endpoints.

As of 28 September 1999, the Health Effects Division has not received this study.

Use of the Pesticide Handler's Exposure Database (PHED)

Cheminova believes that PHED overestimates the potential occupational exposure to ethyl parathion because of the "extra care" that workers take with the use of certain pesticides. Cheminova states that it will conduct exposure studies to demonstrate this belief.

HED agrees that human exposure to pesticides in occupational settings is variable based on the activities and behaviors of the individual handlers. However, much of the exposure cannot be controlled voluntarily by taking "extra care". The Pesticide Handlers Exposure Database unit exposure values are central tendency and do not reflect high-end values. As of 20 September 1999, HED has not received any new exposure studies.

Postapplication Worker Risk Assessment

Cheminova cites several literature studies on ethyl parathion that provide different half-lives than that used in the HED risk assessment. These values range from 0.3 days on cotton in Arizona to 6.9 days on citrus in Florida. In their response to the environmental fate assessment for ethyl parathion, Cheminova uses a 2.9 day foliar

half-life.

Studies cited by Cheminova did not include information concerning application rates and initial residues, two parameters critical for the estimation of reentry intervals. As a rangefinder, HED used an initial residue of 20 percent of the application rate and a dissipation rate of 10 percent per day. This dissipation rate approximates the foliar half-life cited above.

cc: RF, Reg. Std. File, R. Griffin, B. Cropp-Kohlligian, J. Becker, N. Paquette